REMARKS

Claims 1, 3 – 5, and 7 – 16 were rejected under 35 U.S.C. §103(a) as being unpatentable over Beug, Chaudhary et al. and Wu et al.

Applicants respectfully submit that this rejection should be withdrawn for the following reasons.

The present invention provides a delivery system and method for selective delivery of a nucleic acid to a specific population of target cells.

This is accomplished by use of a fusion protein comprising (1) a nucleic acid binding protein, such as protamine, and (2) an antibody which specifically recognizes a cell surface marker on the desired target cell. The nucleic acid is joined to this complex by its interaction with the nucleic acid binding portion of the fusion protein.

The Examiner has contended that the present invention is no different from what is taught in Chaudhary and Wu. Applicants respectfully disagree, because neither teaches the fusion protein of the present invention.

Although the Examiner states at page 5, lines 1-2, that "the use of fusion proteins to selectively target the delivery of nucleic acid molecules to a was **known**" [sic] [emphasis added], this is not supported by the references relied upon. The first reference relied upon, Beug, used a **chemical conjugate** approach, described as "a transferrin-polycation conjugate" in the abstract, lines 3-4, for delivery of a nucleic acid; Beug does not use a fusion protein.

Similarly, Wu also used a **chemical conjugate** approach as depicted in Figure 1, consisting of a nucleic acid bound to a polycation, which is itself non-covalently bound through disulfide bond to a ligand; thus, Wu does not use a fusion protein.

Finally, while Chaudhary does use a fusion protein, it is an entirely different system. The fusion protein delivers a protein (an immunotoxin), not a nucleic acid, to a specific cell type; Chaurdhary does not deliver nucleic acid and does not teach such a system. In view of the fact that the references to delivering nucleic both talk about a chemical conjugate and see no problems with such an approach, there is no motivation in the combination to use a fusion protein to deliver nucleic acid. Therefore the Examiner's statement that the use of fusion proteins to selectively target nucleic acids for delivery was **known** is simply inaccurate.

Applicants have previously submitted a Declaration of Wayne Marasco, a co-inventor of

the present invention and a co-author of Li et al., that describes the surprising advantages of using the fusion protein of the present invention as compared to a chemical conjugate of an antibody and a nucleic acid binding protein.

Applicants respectfully submit that Examiner has not interpreted the results in Li accurately. The Examiner apparently has not appreciated that Dr. Marasco is both a co-inventor of the present invention and a co-author of Li, and thus is in a unique position to describe what the experiments reported therein mean.

The Examiner has taken the position that Li does not provide a direct comparison of chemically linked versus fusion proteins for nucleic acid delivery (see Office Action page 6, lines 4-6), and contends that Li compares "different compositions made through the addition of the components in a different order" (page 6, lines 5-6). This completely ignores comparing the results presented in Figures 6C and 7B of Li.

Figure 6C shows the fusion protein approach, while Figure 7B uses the chemical conjugate approach. The Examiner's statement that Li only compares mixing components in a different order does not consider what the results of both figures teach.

As indicated on the attached exhibit and described in Dr. Marasco's Declaration, paragraph 18, it is absolutely appropriate to compare Figure 6C with Figure 7B. Both experiments use the same antibody, an antibody specific for ErbB2 receptor, which is expressed on the surface of SKBR3 cells but is not expressed on the surface of MCF7 cells. Thus, one would expect this antibody to preferentially target SKBR3 cells. Furthermore, both experiments use the same reporter gene, detected by measuring luciferase activity. Given that these experiments use the same target cells, the same antibody, and the same nucleic acid for delivery, comparison of their results is entirely appropriate.

And given the similarity, one would expect similar results with the two approaches. However, comparing these two experiments clearly shows the increased selectivity afforded by the fusion protein approach for targeted nucleic acid delivery. Figure 6C shows that cellular uptake of the fusion protein is 8 – 10 fold more selective for cells containing the target, ErbB2 receptor (SKBR3 cells). In contrast, in Figure 7B it is clear that the cellular uptake of the conjugate is only 4 – 5 fold more selective in target cells. These data are highlighted on the attached exhibit to remove any confusion regarding the results applicants are relying on. These

are the data that Dr. Marasco referred to in paragraph 18 of his Declaration. Finally, these are the data that establish the unexpected superiority of using a fusion protein, rather than a chemical conjugate approach, to selectively deliver a nucleic acid to a specific cell type.

The Examiner has argued that it would be obvious to use a fusion protein comprising an antibody to target a nucleic acid to a specific cell type, given Beug's chemical conjugates for nucleic acid delivery, Wu's chemical conjugates for nucleic acid delivery, and Chaudhary's fusion protein for protein delivery. Applicants respectfully disagree for the following reasons. As described above, none of these references alone teach the nucleic acid delivery system of the present invention. Furthermore, nothing in these references in any way suggests that a recombinant fusion protein would be more precise in delivery to a specific cell type than a chemical conjugate approach.

Beug does not suggest the present invention's fusion proteins, and in fact specifically teaches away from such an approach. While fusion proteins necessarily use a *fixed* ratio comprising one targeting moiety for each nucleic acid binding moiety (i.e. 1:1), Beug teaches the advantages of being able to *vary* these two components from ratios of 1:4 up to 10:1, a 40-fold range. Thus, nothing in Beug provides the artisan with any motivation or suggestion that a fixed 1:1 ratio is preferable.

Similarly, Wu teaches the use of chemical conjugates, and uses "ligands" to target cells. While both Wu and Beug refer to antibodies in passing, neither focuses on antibodies in any way, including discussing the specific advantages they offer. The Examiner has stated that it was well known in the art that using an antibody gives the "most specific and versatile targeting of any antigen." Both systems were looking at targeting receptors with a ligand and there is no reason why an antibody would be better. Applicants respectfully submit that the Examiner's statement uses impermissible hindsight reconstruction. If the superiority of antibodies for targeting cells was so obvious at the time, it is not clear why none of these references used them or described their theoretical advantages. Indeed, as previously argued, Wu simply lumps antibodies together with polypeptide hormones as an alternative ligand for targeting. Given that polypeptide hormones work through a completely different mechanism, the reference to antibodies for target binding, the mere inclusion of antibodies is at best an afterthought of Wu, rather than a teaching, suggestion, or motivation of their utility for targeted delivery systems.

Turning now to Chaudhary, the skilled artisan would have no motivation to adapt its fusion protein for delivery of a nucleic acid, because it addresses a completely different problem, namely cloning functional antibody genes in E. coli for targeting toxins for cytocidal therapy. The most important difference between the Chaudhary system and the present invention is that the entire Chaudhary system is present in the single fusion protein, whereas the present invention has two components: the fusion protein and the nucleic acid. Thus, in addition to being directed to solving a different problem, there is also nothing in Chaudhary that teaches how to solve the specific problem of getting a nucleic acid to join the fusion protein complex in a sufficiently strong and specific manner to enable targeted delivery. Thus, the improved cloning technique which is the focus of Chaudhary does not teach or suggest the present invention, nor does it motivate the skilled artisan to adapt its fusion protein approach.

Thus, the rejection of the claims should be withdrawn.

Claim 6 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Beug et al. in view of Chaudhary et al. and Wu et al as applied to Claims 1, 3 – 5, and 7 – 16, and further in view of Ryder et al.

Applicants respectfully submit that this rejection should be withdrawn for the following reasons.

Applicants respectfully submit that the addition of Ryder et al. to the combination in no way overcomes the essential deficiency of the references discussed above. As indicated by the Examiner, Ryder discloses sequence specific binding of Jun to a nucleic acid. Ryder in no way discloses targeted delivery of nucleic acids to cells, nor provides any motivation to the skilled artisan. Thus, Ryder cannot cure the fundamental defect in the original combination of references, which do not teach the use of an antibody fusion protein for selective delivery of a

nucleic acid. Accordingly, for the reasons of record which are repeated herein, and for the reasons mentioned above, this rejection of the claims should also be withdrawn.

In view of the foregoing, applicants respectfully submit all claims are in condition for allowance. Early and favorable action is requested.

Respectfully submitted,

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Ronald I. Eisenstein (Reg. No.: 30,628)
NIXON PEABODY LLP
100 Summer Street
Boston, MA 02110
(617) 345-6054